

PRELIMINARY OBSERVATIONS

Antiplatelet treatment with cilostazol after stent implantation

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Abstract

Objectives—To evaluate the efficacy of cilostazol, a new synthetic inhibitor of phosphodiesterase, in preventing stent thrombosis after successful implantation. **Design**—Preliminary prospective study.

Setting—A single coronary care unit in Japan.

Patients—Elective, bailout, or primary stents were implanted in 85 consecutive patients with 93 lesions. Primary stent implantation was performed in 18 patients with acute myocardial infarction. Patients received 200 mg cilostazol and 243 mg aspirin after stenting.

Main outcome measures—Stent thrombosis, major and minor complications, and side effects were assessed in the six months after stenting.

Results—Gianturco-Roubin stents were implanted in 37 lesions, Wiktor stents in 55, and Palmaz-Schatz stents in 27. Multiple stents were used in 26 lesions. There was no mortality, stent thrombosis related Q wave myocardial infarction, emergency bypass surgery, repeat intervention, or vascular complications in the six months of follow up. Acute or subacute closure did not occur after stenting. There were no serious side effects such as leucopenia and/or abnormal liver function for three months. Cilostazol was withdrawn in one patient because of skin rash. Patients who underwent primary stenting had no clinical events, such as acute or subacute thrombosis, or side effects.

Conclusions—Cilostazol is an effective antiplatelet agent with minimum side effects after elective, bailout, or primary stent implantation.

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aspirin and ticlopidine without anticoagulation after native coronary artery stenting has a low incidence of stent thrombosis and vascular access and bleeding complications.⁵⁻⁶ Ticlopidine, however, may cause significant adverse reactions, in particular, neutropenia or abnormal liver function, or both.⁷⁻⁸ Cilostazol, a novel potent inhibitor of phosphodiesterase, has an antiplatelet effect similar to that of ticlopidine and a lower rate of complications in the treatment of peripheral arterial disease.⁹⁻¹¹ This preliminary prospective study aimed to determine whether cilostazol is effective in preventing stent thrombosis after coronary stenting.

Methods

PATIENTS

Between July 1996 and November 1997, 86 consecutive patients were treated with cilostazol and aspirin after coronary stenting to establish a new antiplatelet regimen. We excluded patients who required mechanical ventilation before stenting, those with cardiogenic shock or concurrent medical conditions necessitating chronic anticoagulation, and those with contraindications to aggressive antiplatelet treatment. One patient was excluded because of cardiogenic shock with acute myocardial infarction. Thus 85 patients (93 lesions) were treated with the antiplatelet regimen after successful optimised stent implantation (table 1). Primary stent implantation was performed in 18 patients with acute myocardial infarction.

DEFINITIONS

Successful delivery was defined as placement of the stent at the desired position. Stent placement was classified as: bailout implantation for acute or threatened vessel closure during or after the procedure, implantation for a suboptimal result, elective implantation, or primary stent implantation. Acute closure was defined as occlusion of a vessel with thrombolysis in myocardial infarction (TIMI) grade 1 or 0 flow.¹² Threatened closure was defined as the presence of a significant dissection immediately after angioplasty associated with either reduced flow in the vessel or electrocardiographic evidence of myocardial ischaemia. A suboptimal result was defined as the presence of a visually estimated residual stenosis of greater than 40% after dilatation with or

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Coronary stent implantation reduces the morbidity of acute or threatened vessel closure after coronary angioplasty.^{1,2} Despite the proved benefits of intracoronary stent implantation, bleeding complications arising from a stringent anticoagulation regimen limit increased clinical use.^{3,4} Recent studies have reported that antiplatelet treatment using a combination of

Table 1 Baseline clinical characteristics

Characteristic	n (%)
Male/female	69/16
Mean (SD) age (years)	63 (10)
LVEF < 40%	9 (11)
Acute myocardial infarction	18 (21)
Previous myocardial infarction	34 (40)
Angina pectoris	33 (39)
Previous PTCA	14 (16)
Risk factors	
Current smoker	65 (76)
Hypercholesterolaemia	20 (24)
Hypertension	43 (51)
Diabetes mellitus	27 (32)
Number of diseased vessels	
1	41 (48)
2	32 (38)
3	12 (14)
Indication for stenting (93 lesions)	
Elective	56
Suboptimal	12
Threatened vessel closure	4
Acute vessel closure	3
Primary	18

LVEF, left ventricular ejection fraction; PTCA, percutaneous transluminal coronary angioplasty.

without an associated non-occlusive dissection, but with normal blood flow (TIMI grade 3). Primary implantation for acute myocardial infarction was defined as intentional implantation in the culprit lesion during emergency catheterisation. Implantation was classified as elective when it had been decided before the procedure.

All patients gave written informed consent to participate in the study. The study was performed according to the principles of the declaration of Helsinki and was approved by our institutional review board. Patients were asked to attend six months' follow up.

STENT IMPLANTATION

Coronary angioplasty was performed using conventional techniques with 8 French guiding catheters by the femoral approach. A heparin bolus (5000 U) was given after insertion of the sheath. Patients were not given dextran or dipyridamole. Three different stents were used: Gianturco-Roubin (Cook, Bloomington, Indiana, USA), Wiktor (Medtronic, Minneapolis, Minnesota, USA), and Palmaz-Schatz (Johnson and Johnson Interventional Systems, Warren, New Jersey, USA). Stents were deployed using stent balloon inflation of 8–10 atm after dilatation. Balloon size was chosen carefully with respect to the diameter of the adjacent non-diseased coronary artery (balloon to vessel ratio of 1:1.1 to 1:1.2). High pressure intrastent balloon inflation to optimise stent expansion was performed in 78 lesions after deployment of all stents. Angiography was performed to assess the success of stenting by quantitative estimate of residual stenosis of less than 30% of the lumen diameter within the stent, effectively positioned at the intended site with TIMI grade 3 flow.

POSTPROCEDURE MEDICATION PROTOCOL

Sheaths were removed two hours after stent implantation. Heparin (180 U/kg/day) was infused for three days after a successful optimised result. Patients were treated with a combination of cilostazol (200 mg twice/day)

and aspirin (243 mg/day) immediately after the procedure. Patients with acute myocardial infarction who had primary stenting were administered antiplatelet regimen one day after stenting together with intravenous infusion of heparin (180 U/kg/day) for three days. Patients continued to receive aspirin and cilostazol for three months.

EVENTS AND FOLLOW UP

Major clinical events during six months' follow up were death, emergency bypass surgery, stent thrombosis related myocardial infarction (Q wave or non-Q wave), out-of-hospital stent thrombosis, and vascular complications. Stent thrombosis related Q wave myocardial infarction was defined as documentation of new pathological Q waves (more than 0.04 seconds) in conjunction with increased activity of creatine kinase (CK) to more than twice the upper limit of normal. Stent thrombosis related non-Q wave myocardial infarction was defined as increased activities of cardiac enzymes to more than twice the upper limit of normal without new pathological Q waves. Out-of-hospital stent thrombosis was defined as any unexplained sudden death or myocardial infarction in the stented vessel. Vascular complications were defined as bleeding or haematoma at the access site requiring transfusion, vascular repair, or external compression.

Electrocardiograms were recorded immediately after implantation, then daily for two days. CK activities were measured immediately after the procedure and at two eight hour intervals. Additional electrocardiograms and CK estimations were obtained if patients had recurrent symptoms.

Patients were discharged within seven days after intervention. Patients were seen as outpatients monthly for three months after the procedure. Complete blood cell counts and enzyme measurements were obtained one week after implantation and at each outpatient attendance for three months.

ANGIOGRAPHIC ANALYSIS

The lumen diameter of the coronary artery was assessed quantitatively with a commercially available coronary angiographic analysis system (Mac Heart Database System; Baxter, Tokyo, Japan). Absolute diameter of the stenosis (in millimetres) was determined by use of the guiding catheter as a scaling device. The following measures were taken to standardise the method of analysis: all study frames selected for analysis were end diastolic to minimise motion artefact, and arterial segments were measured between the same identifiable branch points. Lesions were characterised according to the modified American College of Cardiology/American Heart Association score.

Cineangiograms were assessed twice by two independent observers who had no knowledge of the study protocol to minimise interobserver and intraobserver variability. Variation in the observers' readings of reference luminal diameter was 0.04 (0.10) mm. Intraobserver variability was 0.03 (0.11) mm.

Table 2 Angiographic and procedural characteristics

Characteristic	n (%)
Location	
Left anterior descending	42 (45)
Left circumflex	13 (14)
Right coronary artery	31 (33)
Saphenous vein graft	7 (8)
De novo/restenosis	79/14
Chronic total occlusion	10 (11)
Modified ACC/AHA lesion type	
A	12 (13)
B1	19 (20)
B2	49 (53)
C	13 (14)
Reference vessel size	
< 2.5 mm	11 (12)
2.5–2.99 mm	36 (39)
3.0–3.49 mm	30 (32)
3.5–3.99 mm	16 (17)
Stent type and number	
Gianturco-Roubin	37 (31)
Wiktor	55 (46)
Palmaz-Schatz	27 (23)
Multiple stents	26 (28)
Mean (SD) reference diameter (mm)	2.96 (0.50)
Mean (SD) lesion length (mm)	14.3 (10.1)
Mean (SD) minimal lumen diameter (mm)	
Before stenting	0.53 (0.46)
After stenting	2.81 (0.61)
Mean (SD) diameter stenosis (%)	
Before stenting	80.8 (16.7)
After stenting	6.4 (12.9)
Mean (SD) maximum inflation pressure (atm)	13.5 (2.9)
Balloon:vessel ratio	1.12 (0.18)

ACC/AHA, American College of Cardiology/American Heart Association.

DATA COLLECTION

Detailed case report forms were completed for all patients and the data entered into a computerised database. The data are expressed as means (SD).

Results

PATIENTS AND LESION CHARACTERISTICS

Gianturco-Roubin stents were implanted in 37 lesions, Wiktor stents in 55 lesions, and Palmaz-Schatz stent in 27 lesions. Table 2 gives details of the number and size of the implanted stents.

PROCEDURAL CHARACTERISTICS AND

ANGIOGRAPHIC MEASUREMENTS

Multivessel stenting was performed in 20 patients and multiple stents were used in 26 lesions (28%). Table 2 lists quantitative angiographic measurements before and after stenting. The mean reference vessel diameter was 2.96 mm and the balloon to vessel ratio was 1.12. The diameter stenosis decreased from 81% to 6% after stenting.

CLINICAL FOLLOW UP

There were no deaths, stent thrombosis related Q wave myocardial infarction, emergency bypass surgery, repeat intervention, or vascular complications (table 3). Acute or subacute closure did not occur after stenting. One patient developed a non-Q wave myocardial infarction due to distal embolism. There were no serious side effects such as leucopenia and/or abnormal liver function for three months. One patient was withdrawn because of skin rash. Patients who underwent primary stenting had no clinical events, such as acute or subacute thrombosis, or side effects.

Table 3 Frequency of primary clinical and angiographic events at six months' follow up

Characteristic	n (%)
Angiographic events	
Acute stent thrombosis	0
Subacute stent thrombosis	0
Clinical events	
Stent thrombosis related Q wave MI	0
Stent thrombosis related non-Q wave MI	0
Repeat intervention	0
Emergency bypass	0
Death	0
Vascular complications	0
Side effects	1 (1.2)
Leucopenia	0
Skin rash	1 (1.2)
Abnormal liver function	0

Discussion

The results of the present study show the feasibility of antiplatelet treatment with cilostazol and aspirin after stent implantation. The use of intracoronary stents for the treatment of symptomatic coronary artery disease increased after the BENESTENT trial.¹³ The utility of stent implantation, however, is limited by stringent postprocedure anticoagulation that increases vascular and bleeding complications without providing sufficient protection against stent thrombosis.^{3 14} In a subsequent prospective study on coronary stent implantation in which stent expansion was optimised by high pressure balloon dilators the stent thrombosis rate was 1.1% in patients who received antiplatelet treatment only after successful stenting.¹⁵ The results have stimulated increasingly common use of ticlopidine after stent implantation despite the increased risk of neutropenia that occurs in up to 0.8–2.1% of patients.^{7 8 15} Cilostazol is a new antithrombotic agent available for the treatment of peripheral arterial disease in Japan and undergoing clinical trials in the United States.^{10 16 17} Although the number of patients in the present study is relatively small, the results show that treatment with cilostazol and aspirin after stenting is safe and effective.

MECHANISMS OF CILOSTAZOL

Cilostazol inhibits the action of cyclic AMP phosphodiesterase in platelets and the production of platelet derived growth factor in endothelial cells.¹⁰ It suppresses platelet aggregation and release reaction by increasing the concentration of cyclic AMP in platelets. It inhibits primary and secondary aggregation and thus has a different mode of action than aspirin, which inhibits only secondary aggregation. Cilostazol has a significantly more potent antiplatelet effect on ADP induced aggregation than aspirin, and on collagen induced aggregation and arachidonic acid induced aggregation than ticlopidine.¹¹ Cilostazol inhibits thrombotic occlusion in an artificial vessel implanted in the femoral artery of dogs.¹⁸ Moreover, orally administered cilostazol prevents thrombotic occlusion of single bodied Z stents deployed in canine iliac arteries.¹⁹ Multiple possible actions, such as inhibition of platelet aggregation and of the release of platelet derived products, may be involved in the effects of cilostazol after stenting.

ANTIPLATELET TREATMENT WITH CILOSTAZOL AFTER STENTING

Recently, Ochiai *et al* reported that cilostazol was useful as part of an antiplatelet regimen after Palmaz-Schatz stent implantation with stable elective placement, but not with emergency stenting for acute or threatened vessel closure.²⁰ Patient related factors such as acute myocardial infarction may increase the risk of subacute stent thrombosis as they are often associated with intracoronary thrombus. The maximum antiplatelet effect of ticlopidine occurred three to five days after the oral dose of 250 mg twice daily.²¹ This suggests that ticlopidine can be used only for elective percutaneous transluminal coronary angioplasty. In contrast, the maximum antiplatelet effect of cilostazol occurred within one day.¹⁰ Therefore, cilostazol may be an effective antiplatelet agent after primary stenting in patients with acute myocardial infarction.

STUDY LIMITATIONS

The study examined a relatively small number of patients. The favourable outcome will need to be confirmed in a large patient group. There are no reports on whether the combination of aspirin and ticlopidine and of cilostazol and aspirin has a synergistic effect on reducing platelet activation and aggregation. Several reports suggest that the rate of stent thrombosis in patients given only aspirin is higher than in those given aspirin and ticlopidine.²²⁻²⁴ The combination of these two antiplatelet agents may be effective because of their different mechanisms of action.

Intravenous heparin was infused after stenting as patients with acute myocardial infarction were included in this study. Administration of heparin is not a well validated treatment after coronary stenting. Further randomised trials are necessary to investigate such treatment after stent implantation.

CONCLUSIONS

These results provide evidence of the safety and efficacy of cilostazol, a new potent antiplatelet agent, after elective, bailout, or primary stent implantation. Larger population studies are required to confirm that such an approach could be a reliable treatment for the management of patients after stenting.

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